REMARKS

Claims 1, 3-8, 10-46 and 48-54 are pending in the application. Claims 1, 3, 19 and 44 are amended, new claim 55 is added and claim 47 is cancelled without prejudice, herein. No new matter is added by those amendments. Claims 25-43 and 48-54 have been withdrawn from consideration by the Examiner. Accordingly, claims 1, 3-8, 10-24 and 44-46 are pending and under consideration in the present application. Claims 1, 10 and 46 are amended herein. Re-examination and reconsideration of the application is requested.

The present Amendment is responsive to the new Office Action dated March 8, 2006. That Office Action was issued, after Applicant's prepared and filed a Notice of Appeal and an Appeal Brief, responding to the Office Action of July 12, 2005. The new Office Action dated March 8, 2006, withdraws most of the rejections and objections raised in the July 12, 2005, Office Action, but re-opens prosecution to raise several new grounds of rejection that were not previously raised. The new grounds of rejection relate to claim language that has been present in the application claims for years (and, in some cases, from the original 2001 filing of the application), yet the new rejections were not previously raised in any of the five Office Actions received prior to the March 8, 2006, Office Action. Rather, the new grounds have been raised, after the Applicant has successfully overcome previously raised rejections.

In addition, new grounds of rejections have been presented that are based, in part, on the same Valdes et al. reference that Applicant discussed in its Appeal Brief (to successfully overcome previous rejections that were based, in part, on the Valdes et al. reference). Applicant's Appeal Brief addressed and overcame a rejection based on an attempt to combine Valdes et al. with another reference (document titled "Current Protocols in Molecular Biology"). In particular, Applicant overcame that rejection by pointing out that Valdes et al. teaches away from the combination by, instead, teaching to address the peroxide degradation problem by using additives to neutralize the peroxide. Thus, Applicant has already shown that Valdes et al. teaches away from combining other references that describe general mutation processes. However, the new grounds of rejections are based on the Examiner's suggestion to combine Valdes et al. with the Stemmer and/or Hatzinikolaou et al. references in the same manner in which the Examiner previously attempted to combine the Valdes et al. reference with the document titled "Current

Protocols in Molecular Biology." Because the Valdes et al. reference itself (and other prior art of record), teaches away from the claimed invention, the new grounds of rejections based, in part on Valdes et al. are improper for the same reason as set forth in Applicant's Appeal Brief with regard to combining Valdes et al. with the document titled "Current Protocols in Molecular Biology."

In the present Amendment, Applicant has addressed each of the grounds of rejection raised in the new Office Action dated March 8, 2006. In view of the present response, the lengthy prosecution history, the withdrawal of most of the previous rejections, and the recent introduction of a number of new rejections relating to claim language that was present in the claims for years or that are similar to the prior-art rejections that Applicant already overcame in the Appeal Brief, Applicant requests an allowance of the present Application.

Response To Objection To Claim 19:

In the Office Action of March 8, 2006, the Examiner raised a new objection to claim 19, and stated that the name of the organisms recited in the claim should be italicized. In response, claim 19 is amended herein, to recite the organisms in italics.

Response To Rejection Under 35 U.S.C. 101:

In the Office Action of March 8, 2006, the Examiner raised a new ground of rejection of claims 1, 3-8, 10-24 and 44-47 under 35 U.S.C. 101, as being directed to non-statutory subject matter. In particular, the Examiner stated that the claimed methods use a host cell still attached to a host such as a human being, and that the claims read on a human being, which is non-statutory. In response, Applicants note that the phrase "host organisms" has been present in the claims, from the original filing of the application, and was not raised as an issue in any of the previous Office Actions issued in the present application. Applicant respectfully traverses this ground of rejection, as the claims do not recite a "human" host organism. One skilled in the art would be well aware of non-human host organisms that may be employed in connection with the present invention. To expedite the prosecution, applicant has amended claim 1 to recite that the host organisms are "non-human host organisms," which is supported by the original specification (e.g., see page 9, line 19-22, describing examples of non-human host organisms).

Response to Rejections Under 35 U.S.C. 112, second paragraph:

In the Office Action of March 8, 2006, the Examiner raised a new ground of rejection of claim 1 and dependent claims 3-8, 10-24 and 44-47 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated that it is not clear to the Examiner how those skilled in the art can conclude that colonies have active glucose by measuring the concentration of glucose oxidase.

In response, Applicant has amended claim 1 to recite that "determining whether the colonies contain active glucose oxidase comprises: detecting a concentration of active glucose oxidase." The original patent specification describes several manners in which a concentration of active glucose oxidase can be detected. For example, the original patent specification states:

> "In one embodiment, the test for whether active glucose oxidase is present in a given colony comprises an assay which tests the production of peroxide. Peroxide is generated upon glucose oxidase reaction with glucose. In one embodiment, leuco-crystal-violet, a substrate that changes color in the presence of active peroxide, is employed. However, in other embodiments, other substances may also be used such as, but not limited to, aminoantipyrine, and the like.
>
> In other embodiments, other methods can be used to test for the presence of active glucose oxidase. For example, the presence or absence of active glucose oxidase may be ascertainable by checking for fluorescence. The more fluorescent a given colony is, the more likely it is that it contains active glucose oxidase. Those skilled in the art will appreciate that further methods to test for the presence of glucose oxidase can be employed in other embodiments without deviating from the scope or spirit of the invention." (Underline added for emphasis.)(page 10, line 16 through page 11, line 6).

As described in the above-quoted section of the original patent application, the presence or absence of a concentration of active glucose oxidase may be detected in a variety of manners, including using color changing materials (that change color in the presence of peroxide, which is generated by a concentration of active glucose oxidase) or checking for fluorescence (the more

fluorescence, the greater likelihood of the presence of a concentration of active glucose oxidase). Once skilled in the art would be able to ascertain (or detect) whether or not active glucose oxidase exists in a colony, based on the disclosure in the present application and conventional knowledge.

Furthermore, in applying the rejection under 35 U.S.C. 103 (discussed below), on page 9 of the current Office Action, the Examiner acknowledged that Hatzinikoloau et al. discloses a method of measuring glucose oxidase activity and concentration of glucose oxidase (citing pages 372-373). Thus, one skilled in the art would know how to measure glucose oxidase activity.

While the Examiner stated that the concentration of "glucose oxidase" can be measured in many different ways, such measurements do not always indicate whether said enzyme is active. However, the claim, as amended, recites that "determining whether the colonies contain active glucose oxidase comprises: detecting a concentration of active glucose oxidase." As noted above, the original specification provides examples of various manners in which active glucose oxidase may be detected. Accordingly, it is submitted that the original specification supports the language of amended claim 1 and that the claim is clear and definite to one of ordinary skill in the art.

Also, the Examiner stated that it is not clear how the concentrations of the glucose oxidase is measured from the colonies unless the glucose oxidase is first isolated. The Examiner further stated that the claim lacks essential steps of isolation and assaying of the glucose oxidase. This characterization of the claimed subject matter is respectfully traversed. The method of claim 1 need not involve isolation of the glucose oxidase. The method may be carried out in-situ or upon isolation. Thus, the claim need not be amended to require isolation. Accordingly, it is submitted that claim 1 is clear and definite to one of ordinary skill in the art.

In the Office Action of March 8, 2006, the Examiner raised a second ground of rejection of claim 1 and dependent claims 3-8, 10-24 and 44-47 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated that the metes and bounds

of the phrases "desirable properties" and "desired peroxide resistant properties" in the context of the claims is unclear.

This rejection is respectfully traversed, in that one of ordinary skill in the art would understand the cited phrase in the context of the claimed invention. Examples of determining whether or not a colony has desired peroxide resistant properties are described in the patent specification, with respect to embodiments in which colonies are screened for active glucose oxidase, after the colonies have been incubated in peroxide (or peroxide introduced in other manners). As described in the patent specification, "colonies that still have active glucose oxidase, after being incubated in peroxide, may exhibit a desirable peroxide-resistive characteristic." (Underline added for emphasis)(See page 12, lines 1-12 of the present specification.)

One of ordinary skill in the art would be able to define desired peroxide resistance properties and employ embodiments of the present invention to formulate enzymes and determine which colonies have a desirable peroxide resistance properties. One skilled in the art would have a desired property in mind (i.e., a predefined property that is desired). The skilled artisan would not practice the claimed method (or any method of formulating an enzyme) in a vacuum, with no desired results in mind. There would be no purpose in formulating an enzyme, unless the artisan had a predefined, desired property (or set of desirable properties) in mind for that enzyme. Accordingly, to expedite prosecution, claim 1 is amended herein to recite screening the colonies for predefined, desired properties and determining whether the colonies have predefined, desired peroxide resistant properties. It is respectfully submitted that one of ordinary skill in the art would be able to understand and practice the invention, based on a predefined, desired peroxide resistant property that the artisan would seek to have in an enzyme.

In the Office Action of March 8, 2006, the Examiner raised a new ground of rejection of Claims 3, 5 and 10 and dependent claims 11-18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated that the term "functionality" is not clear to the Examiner. It is noted that the term "functionality" was included in the original claims filed in 2001, and was not cited as being an issue in any of the previous Office Actions

issued for the present application. While Applicant believes that the claims are clear and particular, claim 3 is amended herein to expedite the allowance of the application. As amended, claim 3 recites that "functionality, to function as a sensor enzyme in a sensor." The original specification describes testing of glucose oxidase by incorporating the glucose oxidase in a sensor or sensing device. (See, e.g., page 6, lines 12-14; page 14, lines 21-23; and page 15, lines 11-13.) Accordingly, it is respectfully submitted that claim 3, as amended, is in compliance with 35 U.S.C. 112, second paragraph. Claims 5, 10 and 11-18 are each dependent (directly or indirectly) on claim 3 and, thus, are believed to be in compliance with 35 U.S.C. 112, second paragraph, for reasons as discussed above with respect to claim 3.

In the Office Action of March 8, 2006, the Examiner raised another new ground of rejection of claims 6-8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated that it is not clear to the Examiner how those skilled in the art can conclude that colonies have active glucose oxidase by only measuring fluorescence or by using a substance that changes color in the presence of active glucose oxidase. The Examiner stated that the applicants have not set up any control steps and, thus, the method lacks essential steps. This characterization of the claims is respectfully traversed.

The original specification describes examples of materials that change color in the presence of active peroxide that is generated by active glucose oxidase. The original specification also describes that the more fluorescence of a colony, the more likely that the colony contains active glucose oxidase. (See e.g., page 10, line 16 to page 11, line 6.) Once skilled in the art would be able to use one of the disclosed color-changing materials (or other suitable color changing material) to detect the presence of active glucose oxidase and to check for fluorescence to detect the presence of active glucose oxidase, as described in the patent specification.

Embodiments of the present invention may be practiced to formulate an enzymes with predefined desired peroxide resistant properties. Once skilled in the art, with knowledge of such color changing materials and fluorescent properties or other techniques for detecting active glucose oxidase, would be able to readily determine whether a colony exhibits desired peroxide

resistant properties, by evaluating the color change or amount of fluorescence, after the colony has been incubated in peroxide. One skilled in the art would readily understand from the original disclosure that a color change (from one color to another, e.g., to a predetermined color) or a fluorescence level (a level of fluorescence at or above a predetermined amount) would be detectable. One skilled in the art (having knowledge of known techniques for detecting active glucose oxidase) would be able to determine from such techniques whether or not a predetermined, desired peroxide resistant property exists (by detecting if active glucose oxidase exists after incubation in peroxide). Accordingly, it is respectfully submitted that claims 6-8 are in compliance with 35 U.S.C. 112, second paragraph.

In the Office Action of March 8, 2006, the Examiner raised another new ground of rejection of claim 44 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated that it is not clear how the "host organism" in claim 44 differs from the "host organism" of claim 1. Accordingly, claim 44 is amended herein to recite that the host organism comprises a microorganism. Examples of such microorganisms are described in the original specification, for example, at page 9, lines 19-22. It is respectfully submitted that claim 44, as amended, is in compliance with 35 U.S.C. 112, second paragraph.

In the Office Action of March 8, 2006, the Examiner raised another new ground of rejection of claim 47 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated that the phrase "accelerated test environment" is not clear. While Applicant disagrees with the rejection (because accelerated test environments are well known in the art as comprising stressed environments that simulate a longer test period), for purposes of expediting the allowance of the present application, claim 47 is cancelled herein without prejudice or disclaimer. Accordingly, the rejection of claim 47 is moot.

In view of the forgoing, it is respectfully submitted that pending claims 1, 3-8, 10-24 and 44-46 are in compliance with 35 U.S.C. 112, second paragraph. The rejections of those claims is, therefore, respectfully traversed.

Response To Rejections Under 35 U.S.C. 103(a)

Claims 1, 3-5, 12-24 and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al., Stemmer and Hatzinikolaou et al.. This rejection is respectfully traversed.

In particular, neither Valdes et al. nor Stemmer or Hatzinikolaou et al. describe or suggest formulating a glucose oxidase enzyme by mutating glucose oxidases to make them resistant to peroxide degradation. Moreover, one of ordinary skill in the art would not have been led by the prior art of record to mutate glucose oxidase genes, much less to mutate such genes and screen for desired peroxide resistance properties. Such procedures would have been a drastic departure from the state of the art and, without the benefit of the present specification as a guide, would not have been obvious to one of ordinary skill in the art.

The Examiner argues that Valdes et al. teach that glucose oxidases in glucose sensors degrade over time due to hydrogen peroxide. The Examiner acknowledges that Valdes et al do not teach a method of producing mutant glucose oxidase that is resistant to degradation from peroxide. Indeed, the Examiner acknowledges that Valdes et al. teaches a different procedure, wherein chemical agents are used to address peroxide degradation. (Office Action, page 8.)

A method as recited in claim 1 is neither described nor suggested by either of the Valdes et al., Stemmer or Hatzinikolaou et al. references. For example, neither the Valdes et al. reference nor the Stemmer or Hatzinikolaou et al. references describes or suggests formulating a glucose oxidase enzyme by "creating a library of *mutated glucose oxidase* genes" or otherwise mutating glucose oxidases. Similarly, neither of those references describe or suggest "introducing each *mutated glucose oxidase* gene of the library into separate expression vectors", "inserting the expression vectors into host organisms", "growing colonies of the host organisms" and "screening the colonies for desirable properties by determining whether the colonies contain active *glucose oxidase* and determining whether the colonies have desired *peroxide resistant properties*." (See claim 1 in Appendix A, italics added for emphasis).

The Examiner had acknowledged that "Valdes et al. does not teach a method of generating a mutant glucose oxidase genes and screening for mutated glucose oxidases which are resistant to degradation in the presence of hydrogen peroxide." (Final Office Action dated July

12, 2005, pg. 4, ll. 16-18.) Accordingly, the Examiner argues it would have been obvious to combine Stemmer and Hatzinikolaou et al. with the Valdes process.

However, the Examiner cites no suggestion or motivation in either the Valdes et al. reference or the Stemmer or Hatzinikolaou et al. references (or any other prior art) for incubating mutated colonies of glucose oxidase with hydrogen peroxide. In fact, neither Valdes et al. nor the Stemmer or Hatzinikolaou et al. references provide any motivation or suggestion for creating a library of mutated glucose oxidase genes and screening colonies for active glucose oxidase and desired peroxide resistant properties. Indeed, as discussed in depth in Applicant's Appeal Brief, Valdes et al. teach away from such methods by, instead, referring to conventional procedures (using additives for deactivating or destroying hydrogen peroxide and, thus, teach away from such a method, as follows:

> "A long term remedy of the degradation of GOD by H_2O_2 could be the immobilization and attachment of the enzyme to a support that deactivates H_2O_2, as it is being produced. Such as study was conducted by Cho[2], using the peroxide decomposition catalyst, activated carbon. In a study conducted by Carter[19], the best results were obtained with activated carbon, impregnated with ruthenium. This combination was able to destroy hydrogen peroxide and stabilized the enzyme." (Valdes et al., pg. 375, col. 1, l.18 to col. 2, l. 6.)

While the Valdes et al., Stemmer and Hatzinikolaou et al. references, themselves, provide no motivation or suggestion, the Examiner argues that a "reasonable expectation of success" provides motivation. However, without the present disclosure as a guide, one of ordinary skill in the art would not have selected known gene mutation processes and known glucose oxidase purifying, isolating and measuring processes to modify Valdes et al.'s disclosed solution to peroxide degradation of glucose oxidase. Stemmer does not appear to mention glucose oxidase anywhere in its disclosure. Hatzinikolaou et al. fails to provide any motivation or suggest any relation to a gene mutation procedure or of addressing peroxide degradation of glucose oxidase.

The Examiner's conclusory statements of motivation to combine and the Examiner's argument of "reasonable expectation of success" fail to address the significant issue of why one skilled in the art would have been motivated to select a process as described by Stemmer, to change the direction taken by those most skilled in the prior art as described by Valdes et al. The Examiner's argument that a "reasonable expectation of success" would have motivated the

combination (Final Office Action, pg. 5, ll. 15-21), is contrary to the express teachings of the prior art. The prior art teaches that those most skilled in the art were taking a wholly different direction to address peroxide degradation of glucose oxidase and, thus, would have found it unreasonable (not reasonable) to change the course of direction from that of the state of the art.

In particular, Valdes et al. refers to conventional, known "additive" methods for addressing peroxide degradation of glucose oxidase. Mutation of glucose oxidase genes and screening of mutated glucose oxidase for hydrogen peroxide resistant properties would have been a drastic departure from the state of the art and, without the benefit of the present specification as a guide, would not have been obvious to one of ordinary skill in the art.

More specifically, Valdes et al. refer to completely different directions taken by those most skilled in the art, whereby the glucose oxidase enzyme is immobilized and attached to a support that deactivates peroxide. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ... would be led in a direction divergent from the path that was taken by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999). Valdes et al., directly refers the reader to conventional methods of addressing peroxide degradation of glucose oxidase that employ additives for destroying or neutralizing peroxide (which is quite different from creating a library of mutated genes and screening for desired peroxide resistant properties). As taught by Valdes, et al:

> "A long term remedy of the degradation of GOD by H_2O_2 could be the immobilization and attachment of the enzyme to a support that deactivates H_2O_2, as it is being produced. Such as study was conducted by Cho[2], using the peroxide decomposition catalyst, activated carbon. In a study conducted by Carter[19], the best results were obtained with activated carbon, impregnated with ruthenium. This combination was able to destroy hydrogen peroxide and stabilized the enzyme." (Valdes et al., pg. 375, col. 1, l.18 to col. 2, l. 6.)

Not only does Valdes et al. fail to teach or suggest to mutate glucose oxidase and screen mutated glucose oxidase for peroxide resistance properties, but, in the above-quoted statement, Valdes et al. further teaches to use other, very different procedures (conventional in the art) to address degradation effects of peroxide on glucose oxidase. Thus, the Valdes et al. reference shows that the direction taken by those most skilled in the art involved employing materials, additives, or the like that deactivate peroxide.

Additional prior art of record also describes conventional "additive" processes for removing or neutralizing peroxide such as by adding an antioxidant or peroxidase to the glucose oxidase to break down peroxide or by coating the glucose oxidase enzyme with a protective coating, including U.S. Patent No. 6,689,265 to Heller et al. (Exhibit B.3) and the article titled "Glucose ENFET doped with MnO_2 powder" by Yin et al (Exhibit B.4.). Those prior art references further emphasize that the direction taken by those skilled in the art for addressing the peroxide degradation of glucose oxidase is wholly different from the direction of the present invention. In U.S. Patent No. 6,689,265 to Heller et al., a peroxide generating enzyme may include a sufficiently thick, natural, electrically insulating protein or glycoprotein layer. (See column 6, lines 59-67 of the Heller et al. patent, Exhibit B.3.) Heller et al. also disclose an alternative embodiment in which a peroxide generating enzyme is immobilized in a non-conducting inorganic or organic polymeric matrix. (See column 7, lines 3-11 of the Heller et al. patent, Exhibit B.3.) Also, Heller et al. describe a first layer enzyme 11 (peroxidase) that reduces peroxide generated from a second layer (glucose oxidase layer) 13. The Yin et al. article describes the addition of MnO_2 to catalyze peroxide and produce water and oxygen therefrom. (Yin, Exhibit B.4, Abstract and pg. 188, col. 1, ll. 20-34.)

Thus, both the Heller et al. patent and the Yin et al. article show that the direction taken by those skilled in the art is to provide additives or complex multi-layer sensor structures to remove hydrogen peroxide. These references, in addition to Valdes et al.'s express references to conventional uses of additives, show that those skilled in the art were not considering mutating glucose oxidase genes and growing and screening colonies for peroxide resistance, but instead were attempting to address the peroxide production issue by removing or neutralizing peroxide with additives (not by altering the glucose oxidase). The state and direction of the prior art, as evidenced by Valdes et al., Heller et al. and Yin et al., was a wholly different direction than that taken by the present Applicants (including creating a library of mutated glucose oxidase enzyme genes and screening colonies for desirable properties by determining whether the colonies contain active glucose oxidase and determining whether the colonies have desired peroxide resistant properties.)

The fact that the primary reference (Valdes et al.) teach away from the clamed invention and the combination suggested by the Examiner, shows that a *prima facie* case of obviousness has not been raised. Numerous Federal Circuit decisions recognize that an invention will not be deemed obvious in a patent law sense when one or more prior art references "teach away" from the invention. For example, the Federal Circuit stated "as a useful general rule, that references that teach away cannot serve to create a prima facie case of obviousness." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354, 60 USPQ2d 1001 (Fed. Cir. 2001).

Furthermore, "an applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." *In re Peterson*, 315 F.3d 1325, 1331, 65 USPQ2d 1379 (Fed. Cir. 2003). Also see, *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990)(the closest prior art reference "would likely discourage the art worker from attempting the substitution suggested by [the inventor/patentee]") and *Singh v. Brake*, 317 F.3d 1334, 1346, 65 USPQ2d 1641 (Fed. Cir. 2003)("whether or not a reference 'teaches away' from a claimed invention" is "relevant in determining whether or not a claimed invention would have been obvious").

Without the present disclosure as a guide, one of ordinary skill in the art would not have found Valdes et al.'s discussion of the degradation of glucose oxidase as a prompt or suggestion to employ a mutation process as described in the Current Protocols in Molecular Biology reference to mutate glucose oxidase genes. Instead, as noted above, one of ordinary skill in the art would have looked to conventional manners of removing peroxide, such as additives for removing or neutralizing peroxide. Accordingly, the rejection of 1, 3-5, 8, 19-24 and 44-47 under 35 U.S.C. 103(a) is further respectfully traversed.

When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. (underline added for emphasis.) *See, e.g., McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351—52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ("the central question is whether there is reason to combine [the] references," a question of fact drawing on the *Graham* factors).

Conclusory statements that prior art references provide motivation to combine, or statements of motivation derived from the Applicant's own specification, are not sufficient to set forth a *prima facie* case of obviousness. "The factual inquiry whether to combine references must be thorough and searching." *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.,* 229 F.3d 1120, 1124— 25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (quoting *C.R. Bard. Inc., v. M3* Systems, *Inc.,* 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak,* 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance,* 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine,* 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("'teachings of references can be combined *only* if there is some suggestion or incentive to do so.') (emphasis in original) (quoting *ACS Hosp.* Sys., *Inc. 'v. Montefiore Hosp.,* 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

As noted above, the Examiner has not shown any motivation or suggestion in the prior art that would have led one skilled in the art to select a mutation and screening process described by the Stemmer for creating a library of mutated glucose oxidase and screening colonies for peroxide resistant properties. In fact, Valdes et al and other prior art of record show that a selection of a mutation and screening process would have been a drastic diversion from the direction taken by those most skilled in the prior art.

The legal authority expresses the requirement for a showing of specificity in the prior art of motivation to select components to combine. *See, e.g., In re Kotzab,* 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed"); *In re Rouffet,* 149 F.3d 1350, 1359, 47

USPQ2d 1453, 1459 (Fed. Cir. 1998) ("even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination. In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); *In re Fritch,* 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (the examiner can satisfy the burden of showing obviousness of the combination "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references").

Because the Examiner has not shown any motivation or suggestion in the prior art that would have led one skilled in the art to select Stemmer's mutation process with the Valdes et al. reference, the Examiner has not raised a *prima facie* case of obviousness. Therefore, the rejection of 1, 3-5, 12-24 and 44-45 under 35 U.S.C. 103(a) is respectfully traversed.

Claims 6-8, 10,. 11 and 46-47 were rejected under 35 U.S.C. 103(c) as being unpatentable over Valdes et al., Stemmer and Hatzinikolaou and further in view of Wagner. The rejection of claims 6-8, 10, 11 and 46 is respectfully traversed, at least for reasons as discussed above with respect to parent claim 1. The Wagner reference does not address the above-noted distinctions between the claims and the Valdes et al., Stemmer and Hatzinikolaou references. Indeed, the Wagner reference was cited, according to the Examiner, for disclosing a method of determining glucose oxidase activity via a sensor by measuring fluorescence emission from a dye, wherein oxidation of glucose by active glucose oxidase reduces the flurescence emission. However, Wagner does not teach or suggest formulating a glucose oxidase enzyme by mutating glucose oxidases to make them resistant to peroxide degradation. Accordingly, the combination of Wagner with the above-discussed references (the Valdes et al., Stemmer and Hatzinikolaou references) would not lead to the presently claimed invention. The rejection of claims 6-8, 10, 11 and 46 is, therefore respectfully traversed. The rejection of cancelled claim 47 is moot.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check

being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date: August 8, 2006

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